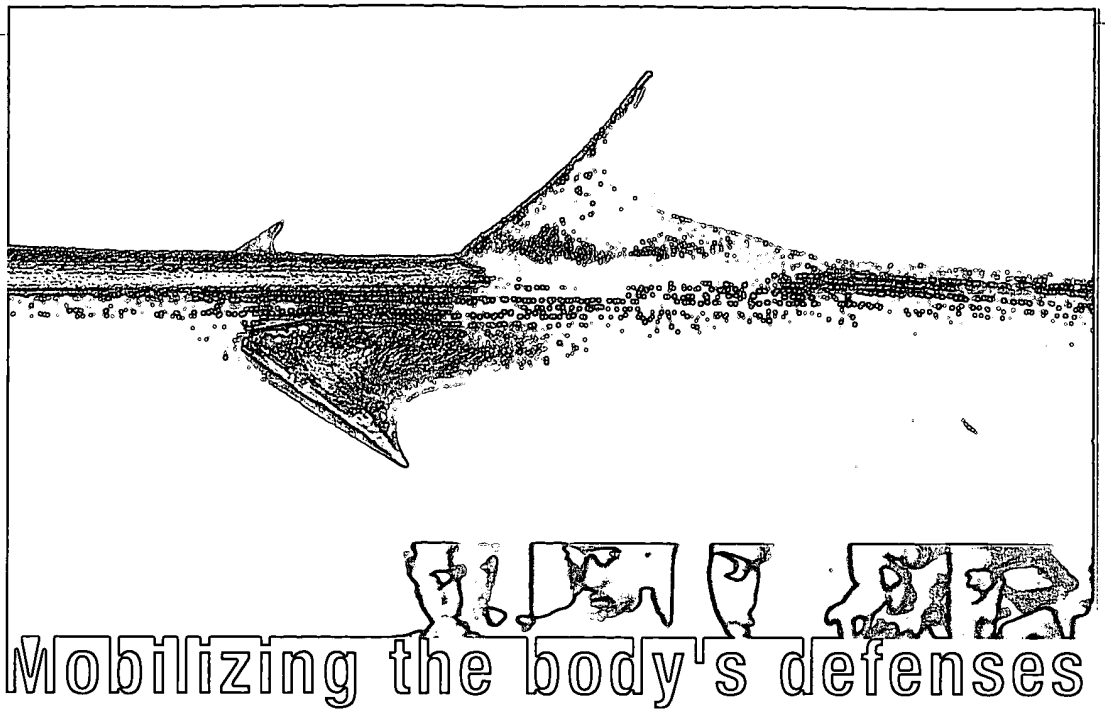
3/03

fact sheet IGN101



Mobilizing the body's defenses

IGN101 ANTI EpCAM CANCER VACCINE

IGN101 is an innovative anti EpCAM cancer vaccine for the therapy of epithelial cancers; these account for approximately 70% of all cancer cases. Its novel mode of action is based on the induction of an immune response against carcinoma cells. This immune response may lead to selective destruction of disseminated tumor cells and thus may slow or prevent the formation of metastases. .

KEY PROPERTIES

- Mimotope antibody vaccine (Target: EpCAM)
- Active cancer immune therapy
- Therapeutic use for epithelial cancer
- Tolerability, immunological proof of concept (Phase I, II)
- Clinical trials designed for product registration ongoing

igeneon

Immunotherapy of Cancer

EXHIBIT 1

was completed in July, 2003. Unblinding of study and interim results are expected for January, 2004.

- A placebo-controlled, double blind pivotal Phase II/III trial in up to 760 patients with adjuvant non-small cell lung cancer (NSCLC) stage IIa, IIb and IIIa; vaccinations start immediately after surgery. Primary objective is relapse free survival. The study started in November 2001 in Freiburg, Germany (principal investigator Prof. J. Hasse) and more than 20 additional centers in Europe. Study duration is app. 4 years, interim evaluations are foreseen. A statistically significant relapse-free survival advantage will serve as a basis for registration. An interim evaluation (first 100 patients) conducted by an independent review board to monitor safety and immunogenicity data of these patients resulted in a recommendation to continue the study: No drug related serious adverse side effects were observed. High immunogenicity was demonstrated: 49% of the patients seroconverted (1:1 placebo:IGN101), coming close to the theoretical optimum of 50% immune response.

Further clinical strategy

A further Phase III study in colorectal cancer is currently at advanced stages of preparation.

The key objectives for igeneon are early proof of clinical efficacy and rapid approval of its products. When early clinical trials suggest evidence of clinical efficacy (based on surrogate efficacy parameters such as disseminated tumor cells in blood and bone marrow and tumor markers), igeneon conducts simultaneous pivotal studies in different clinical indications in an effort to reduce the time to registration and to maximize the chance of success.

Study characteristics

Ongoing studies

Phase/ Study design	Indication(s)	Number of patients (total)	Country, region/ Center(s)	Head of study	Goal of study/ Clinical endpoints	Status
I / Open label	Epithelial tumors	18	Austria/University Clinic Graz	Hellmut Samonigg	Exploratory/Safety and tolerability, immunological parameters, circulating tumor cells	Completed
II / Open label	Epithelial tumors	48	Austria/University Clinic Graz	Hellmut Samonigg	Exploratory/Immunological parameters in combination with chemotherapy	Completed
II / Open label	Epithelial tumors	45	Europe/4 centers	Hellmut Samonigg	Circulating tumor cells in blood	Recruiting
II / Placebo-controlled	Epithelial tumors	220	Marocco/Hôpital Avicenne, Rabat	Abdellatif Settaf	Exploratory/Overall survival, safety, immunogenicity	Recruiting completed
II/III / Placebo-controlled	Non-small cell lung cancer	up to 760	Europe/Freiburg and elsewhere	Joachim Hasse	Approval/Relapse-free survival, total survival	Recruiting

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IGENEON
Brunner Strasse 69/3, 1230 Vienna, Austria
phone: +43-1-90 250,
fax: +43-1-90 250-901
www.igeneon.com

Corporate Communications contact:
Ursula Mayer
ursula.mayer@igeneon.com

Scientific contacts:
Hans Loibner, CEO
hans.loibner@igeneon.com

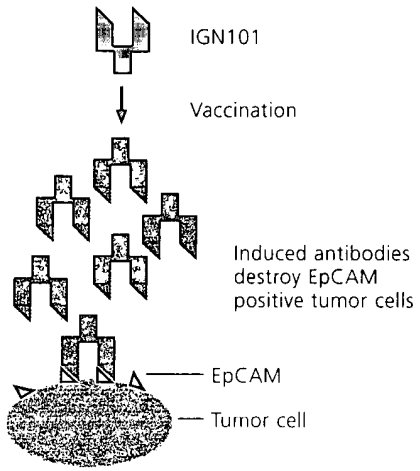
Gottfried Himmler, CSO
gottfried.himmler@igeneon.com

MODE OF ACTION

IGN101 consists of a xenogeneic (foreign) protein used as vaccine antigen in an immunogenic formulation. This xenogeneic vaccine antigen is the murine monoclonal antibody 17-1A.

IGN101 has structural epitopes (mimotopes) related to EpCAM (Epithelial Cell Adhesion Molecule) and elicits an immune response that is directed towards the vaccine antigen and because of its structural similarity, towards EpCAM.

Antibodies induced by vaccination with IGN101 recognize epithelial cancer cells as "foreign" and activate effector functions such as complement-dependent cytotoxicity (CDC) and antibody dependent cellular cytotoxicity (ADCC). These effector mechanisms may be directed to eliminate single carcinoma cells disseminated from the primary tumor.



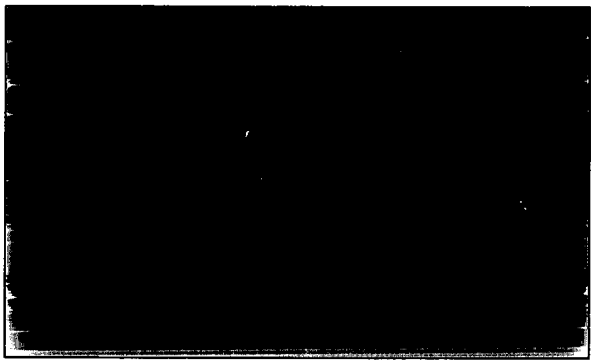
EpCAM is a cell surface glycoprotein present on normal epithelial cells and overexpressed on the majority of epithelial cancers. Examples include: gastric adenocarcinoma, carcinoma of the small intestine, colorectal adenocarcinoma, pancreatic carcinoma, cholangiocarcinoma, biliary duct carcinoma, lung carcinoma, renal cell carcinoma, transitional cell carcinoma of the bladder, thyroid carcinoma, prostate carcinoma, ovarian carcinoma, endometrium carcinoma, squamous cell carcinoma of the cervix, adenocarcinoma of the cervix, mammary carcinoma and epitheloid mesothelioma. EpCAM mediates homophilic adhesion of cells and may be involved in the mediation of cellular growth/developmental signals.

THERAPEUTIC CONCEPT

In Western industrialized countries, tumors of epithelial tissues are the most common form of cancer (incidence: 70%). Early dissemination of malignant cells from primary tumors to secondary sites (a process that is generally occult at the time of primary diagnosis) is probably one of the major mechanisms for metastatic relapse and fatal progression of disease. Chemotherapy often fails to attack these cells because they do not divide. Recent studies provide evidence for an immunotherapeutic role in the elimination of disseminated tumor cells preventing or delaying the development of metastases.

Subcutaneous injections with small amounts of murine 17-1A adsorbed on aluminum hydroxide (=IGN101) elicit a humoral immune response against EpCAM positive tumor cells. This immune response may reduce or eliminate disseminated tumor cells.

Our vaccination approach aims to provide therapeutic intervention to prevent the development or further spread of metastases.



Disseminated tumor cells in peripheral blood of a cancer patient

CLINICAL TRIALS

- **Phase I clinical trial on IGN101: completed in 2001**
- **open-label Phase II clinical trial: completed in 2002**
- **Phase II and Phase II/III studies in progress**

Phase I clinical trial completed

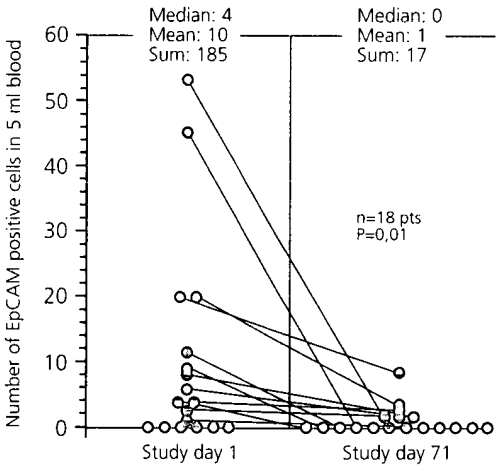
A **Phase I clinical trial** with IGN101 was completed at the Medical University Clinic Graz, Austria in 2001. 18 patients with biopsy proven carcinoma that failed conventional therapy or were deemed refractory to standard agents, were enrolled. Patients received 0.5 mg IGN101 subcutaneously on days 1, 15, 29 and 57.

Immunological assessments included the total humoral immune response, the IgG/IgM level and the amount of EpCAM specific antibodies. Evidence of anti-tumor effects were assessed by determination of the number of EpCAM positive tumor cells in blood measured on days 1, 29 and 71.

Results

- **Excellent tolerability:** The only side effects seen were mild to moderate transient erythema (reddening of the skin) at the injection site, no systemic side effects were observed
- **High overall and specific immunogenicity:** Seroconversion occurred in all patients and a secondary IgG antibody response was induced, indicating T-cell help and memory. In all patients anti-EpCAM IgG was induced. A mean anti-EpCAM IgG level of 9 µg/ml was achieved (> 5-31 µg/ml).
- **No influence of prior chemotherapy (CT) on immunogenicity:** 12/18 patients received CT prior to vaccinations. These patients showed a similar overall and specific immune response compared to those without CT
- **Early indication of efficacy:** The number of circulating EpCAM+ cells in blood significantly decreased during the vaccination course. Furthermore, in some patients a decrease or stabilization of tumor markers was seen. 15/18 patients showed stable disease for at least 2 months.

Reduction of EpCAM positive cells



EpCAM positive cells in 5 ml blood were detected by paramagnetic mAb HEA125 (MACS separator) after lysis of erythrocytes.

Phase II clinical trial completed

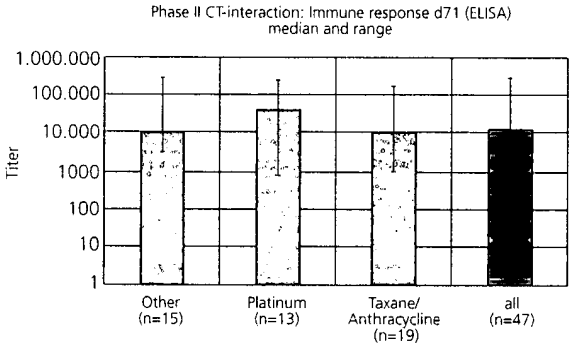
A **Phase II clinical trial** was completed in 2002 at the Medical University Clinic Graz, Austria. The object of the study was to assess the influence of concomitant CT on immunogenicity of IGN101 in patients with carcinoma likely to express EpCAM. Three different, commonly used CT regimens, grouped into anthracyclins and/or taxanes, platinum containing regimens and other CT, were analyzed. 42 patients received 0.5 mg IGN101 subcutaneously on study days 1, 15, 29 and 57; first CT treatment was initiated on study day 1.

The primary objective was to evaluate the specific immunogenicity of repeated vaccinations with IGN101. The second objective was to monitor safety and tolerability in cancer patients treated with multiple doses of IGN101 with concomitant chemotherapy.
Immunological assessments were the same as for Phase I (see above).

Results

- **Specific immunogenicity comparable to results of Phase I:** All 42 patients raised antibodies against the vaccine antigen. 40 patients seroconverted, 21 after 2 vaccinations, and 19 after the 4th. The mean mAb 17-1A specific IgG concentration was 86 µg/ml serum; mean EpCAM specific IgG concentration was 6 µg/ml (2-42 µg) serum.
- **No significant negative impact of concomitant chemotherapy:** There was no significant negative influence of concomitant chemotherapy on overall as well as on specific immunogenicity of repeated vaccinations with IGN101.

Influence of different CT on total immune response



Ongoing clinical program

Several further IGN101 studies have started to substantiate and prove this therapeutic concept:

- A multi-center, open-label Phase II trial in 45 patients with epithelial cancers. Primary objective is assessment of surrogate efficacy of IGN101 against circulating tumor cells in blood. The study started in Q4/2002 at the Medical University Clinic Graz, the University Clinic Innsbruck, The General Hospital (AKH) Vienna, Austria and the Charité, Berlin, Germany.
- A placebo-controlled, double blind Phase II trial in 220 patients with three epithelial cancers (lung, colorectal, esophageal/gastric cancer) stage III and IV. Clinical end point is overall survival. The study started in September 2001 in Rabat, Marocco (Prof. A. Settaf). Recruitment

IGN101

First survival benefit results

A placebo controlled, double-blind phase II trial with IGN101 in 220 patients with three epithelial cancers (lung, colorectal, esophageal/gastric cancer) stage III and IV is being conducted. The study started in September 2001 in Rabat, Morocco (Prof. A. Settaf). Patient recruitment ends in May 2003. Study end is expected end 2003. Clinical end point is overall survival.

A blinded analysis of immune responses was performed with sera of 100 colorectal patients. 50.4% of the patients had proven immune response (50% is the theoretical number based on 1:1 randomization of placebo-and verum- treated patients).

Furthermore the immune response results were correlated in a blinded fashion with survival:

The **1 year survival rate** of the CRC IV patients without immune response (n=22) is **45%**, corresponding well to a huge database (Cochrane Library 2003, issue 1; corresponding value 44.3%). The **1 year survival rate** of the CRC IV patients with a proven immune response to IGN101 (n=23) amounts to **85%**. This difference is statistically significant (p=0.005). The corresponding Kaplan-Meier survival curves are shown in the following figure. Patients in both groups are well balanced with regard to Karnofski performance status, liver enzyme values and treatment by concomitant chemotherapy.

A statistician´s report including Kaplan-Meier survival curves and calculation of significances (log-rank, Gehan, Cox-regression) is available as confidential information.

CRC IV (n=45):

Survival based on immune response